NIH HEAL Workshop: Target Validation for Non-Addictive Therapeutics Development for Pain

October 19-20, 2020

Session Framing Questions

Session A - Human Evidence for Target Validation

Co-Chairs:
Andrea Houghton & Narender Gavva

Session Participants:
Ted Price - Ralf Baron - Jordi Serra - Martin Koltzenburg - Franziska Denk - Luda Diatchenko
Paul Miller - Myung Kyun Shin – Pascal Laeng (NIH Liaison)

Framing Questions:

- ✓ How to build confidence that the target is pivotal in pain processing and pathophysiology of disease?
- ✓ How can you use genetic data to mine for novel targets (and potential AEs)?
- ✓ How can profiling human tissue enable the discovery of novel targets (and potential AEs)?
- ✓ Can QST in patients reveal mechanisms that could lead to target discovery?
- ✓ Can electrophysiology in patients be utilized for target validation?

Session B - Tools and Models to Test Hypotheses *in vitro*

Co-Chairs:
Seena Ajit & Aj Kaykas

Session Participants:
Clifford Woolf - Marc Ferrer - Owen McManus - Mark Varney – Rachel Groth - Max Salick – Ci Chu - Jamie Driscoll (NIH Liaison) – Sitta Sittampalam (NIH Liaison)

Framing Questions:

Translatability of tools and models: from in-vitro (animals/tissues/organoids) to humans:

- ✓ What questions are human cell models (iPSC, organoids) most appropriate for, what are questions where they may not be the best choice?
- ✓ What are the gaps that need to be filled to optimize these models for drug development, specifically for target ID/target validation in pain using these models?
- ✓ How do we select relevant/meaningful phenotypes/endpoint measures?

Validity of the in-vitro models and technologies (e.g. hiPSCs to sensory neurons, CRISPR, role for other neuronal cells in complex 3D cultures etc.):

- ✓ How well hiPSC derived sensory/DRG/CNS neurons functionally mimic primary human neurons of the same origin?
- ✓ Can useful biomarkers, mechanisms and pain circuitry be identified from animals or hiPSC-derived 3D organoid/tissue models? (for human applications).
- ✓ What new approaches (genetic, proteomic and epigenetic) are there to validate *in vitro* models to human clinical trials?

Affordability of the models and tools:

- ✓ Much of the current in-vitro technologies (MEA, High content screening, Ephys HTS, etc.) are quite expensive. Are there consortia that provide such services to academic scientists at reasonable costs?
- ✓ Which tools are available to academic groups, what does the field need to make this possible? (think NCRCRG but for pain) https://www.nimh.nih.gov/research/research-funded-by-nimh/therapeutics/national-cooperative-reprogrammed-cell-research-groups-ncrcrg-to-study-mental-illness.shtml)
- ✓ Is there a 'library" of validated intrinsic and synthetic molecules (approved drugs and chemical probes) to be used as tools to interrogate new targets and pathways identified using the above tools?
- ✓ What areas of emerging tools and technologies require funding for target validation in non-addictive pain therapies?

Session C - Tools and Models to Test Hypotheses *in vivo*

Co-Chairs:
Annemieke Kavelaars & Gordon Munro

Session Participants:
Greg Dussor - Cheryl Stucky - Camilla Svensson - Andrew Rice - Thomas Christoph - Mark Urban – Frank Porreca - Sarah Woller (NIH Liaison)

Framing Questions:

- ✓ What are the best, state of the art tools for confirming target engagement and target validation?
- ✓ Do we need bioassays and/or surrogate markers in addition to behavioral outcomes?
- ✓ How important are the understanding of PK/PD, formulation, and compound stability to *in vivo* target validation?
- ✓ How important is it to establish a therapeutic index, identify off target effects, and assess safety and analgesic tolerance? How should this be done if it is considered a selling point?
- ✓ What level evidence of reproducibility would be needed?